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AN UPDATE ON MEASUREMENT AND MONITORING OF COUGH: WHAT ARE THE IMPORTANT STUDY ENDPOINTS?

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Abstract

There has been considerable progress in the development of tools that assess cough. The Visual Analogue Scale for cough severity is widely used and it is brief and practical for use in the clinic. The Leicester Cough Questionnaire (LCQ) and the Cough-specific Quality of Life Questionnaire (CQLQ) are the most widely used health status questionnaires for adult patients with chronic cough. They are well validated for assessing the impact of cough. Cough can be assessed objectively with challenge tests that measure the sensitivity of the cough reflex. Cough challenge tests are better used to determine the mechanism of action of therapy, rather than efficacy. Cough frequency monitoring is the preferred tool to assess cough objectively, and they are increasingly being used as primary end-points in clinical trials. The most widely used cough monitors are the Leicester Cough Monitor (LCM) and VitaloJak. They are ambulatory devices that consist of a microphone and recording device. Cough frequency monitors do not reflect the intensity or the impact of cough; hence their relationship with subjective measures of cough is weak. Cough should therefore be assessed with a combination of subjective and objective tools. There is a paucity of studies that have investigated the minimal important difference of cough frequency monitors; this deserves further investigation.

Keywords: cough, cough intensity, monitoring, measurement, quality of life

Introduction

Cough is associated with significant physical and psychological morbidity.(1) An assessment of cough severity is important in the clinic because it is used to evaluate the response to trials of therapy.(2) It is also important in clinical trials that evaluate the efficacy of anti-tussive medications.(3) The severity of cough can be measured by several methods; symptom severity, frequency, intensity and impact on quality of life. A number of validated tools are now available to assess cough (Table 1). A combined subjective and objective assessment is necessary for comprehensive evaluation.(4) This review article will focus on the measurement and monitoring in adult patients with chronic cough.

Visual Analogue Scales

Visual Analogue Scales (VAS) are widely used for the subjective assessment of cough because they are brief and easy to use.(5) The subject is asked to mark on a 100mm scale between 'no cough' and 'the worst cough severity'. The advantage of VAS is that they assess the symptom in isolation and reflect the severity. They are also freely available. The VAS is likely to be valid for use in research studies. There is however, a lack of published data reporting its validity and the minimal important difference. The VAS has also been evaluated in acute and sub-acute cough.(6;7) The minimal important difference (MID) has been reported to be 17mm in acute cough.(6) The MID for VAS in chronic cough is likely to be similar to that of acute cough in the authors' opinion but this has not been studied. The VAS is highly responsive to change.(8) In the authors' opinion, the use of VAS should be encouraged because it is familiar to clinicians, brief and clinically meaningful. Furthermore, similar tools are used effectively in the management of other symptoms such as chest pain. The benefits of using the VAS include improved communication between clinicians

regarding the severity of cough and documenting longitudinal observations. The VAS can also be used to assess the urge, frequency and intensity of cough.

Health Related Quality of Life

Cough can have a wide-ranging impact on the patient, and is very disruptive. It can lead to physical symptoms such as syncope, chest pain, urine incontinence, vomiting, headache and sleep disturbance. It is associated with psychological morbidity such as anxiety and depression and socially it can lead to embarrassment and disruption of activities. Health-Related Quality of Life (HRQOL) can be quantified by using specifically designed questionnaires. Their advantage in comparison to VAS scales is that they capture the wider impact of cough on the individual. HRQOL questionnaires provide a structured and standardised approach to quantifying health status. They are well validated for this purpose and highly responsive to change.(9) HRQOL questionnaires can be categorised into generic tools, such as the SF-36 or SGRQ (St George's Respiratory Questionnaire) or disease specific. A limitation of generic tools is that they are generally longer questionnaires and potentially less responsive to change. It is advisable to use cough-specific HRQOL questionnaires for the assessment of health status in patients with cough. The two most widely used HRQOL questionnaires for adult patients with chronic cough are the Leicester Cough Questionnaire (LCQ) and Cough-Specific Quality of Life (CQLQ).(10;11) For children, a recently validated questionnaire is now available, Paediatric Cough – Quality of Life Questionnaire (PC-QLQ).(12)

Leicester Cough Questionnaire (LCQ)

The LCQ is a 19-item questionnaire comprising three health domains; physical, psychological and social.(10) It is brief, easy to use and score. It was developed using a patient-rated importance scale, also known as a clinimetric method. It was developed for patients with chronic cough but has also been validated for patients with Chronic Obstructive Pulmonary Disease (COPD), bronchiectasis and acute cough.(13-15) It is the most widely used of all cough HRQOL questionnaires, since 2001. It has been translated into a wide range of languages. The LCQ has been well validated and has very good internal reliability, repeatability and responsiveness.(10) The minimal important difference in acute and chronic cough are 2.0 and 1.3 respectively.(6;15) The LCQ has been used in clinical trials of Erythromycin, Gabapentin, cough suppression physiotherapy and Interferon therapy. It is currently being used in a clinical trial of Transient Receptor Potential Ankyroid Receptor Type 1 inhibitor.

Cough-specific Quality of Life Questionnaire (CQLQ)

The CQLQ is a 28-item questionnaire with 6 domains, developed in the United States of America.(11) It was also developed using clinimetric methodology. The CQLQ is well validated in chronic cough, acute cough and Idiopathic Pulmonary Fibrosis (IPF). It has good internal reliability, repeatability, responsiveness and the minimal important difference in chronic cough is 13 units.(16) It has recently been used in a clinical trial of Esomeprazole in chronic cough and Thalidomide in patients with cough associated with IPF.(17;18)

Other Subjective Questionnaires

Cough Severity Score (CSS)

The CSS is a two-part question referring to symptoms during the day and night time.(19) The response scale captures cough frequency, intensity and overall impact. There is little clinical experience with this tool and the minimal important difference has not been reported. Further studies of this tool are underway.

Cough Severity Diary (CSD)

CSD is a brief tool, comprising 7 items.(20) It was developed using feedback from patients. In addition to severity, it captures the impact of cough intensity. There is, however, little clinical experience with this tool. The minimal important difference has not been studied.

Objective assessment of cough

There has been significant progress recently in the development of objective tools to assess cough. The clinical use of objective tools is to validate the presence of cough in subjects and evaluate the improvement following therapy. Until the development of cough monitors, assessment of cough reflex sensitivity was the only objective method being used. The limitation of cough reflex sensitivity measurement is that it only assesses the mechanism of cough, not the efficacy from the patient's perspective. The recent technological advances in recording devices have led to significant achievements in the field of cough detection monitoring. There is general consensus that the assessment of cough frequency is the gold-standard objective tool.(21) It is also possible to measure cough intensity with physiological measures, but they are invasive, and not practical for the clinical setting.

Cough Reflex Sensitivity – the Cough Challenge Test

The methodology to measure the sensitivity of the cough reflex is, in principle, similar to that used to assess bronchial responsiveness with agents such as methacholine. Cough is provoked by the inhalation of nebulised tussive agents, usually capsaicin or citric acid. Other tussive agents that can be used include tartaric acid, fog, cinnamaldehyde and bradykinin. The outcome measure is usually expressed as the concentration of tussive agent that causes two or five coughs, C2 or C5. Cough reflex sensitivity assessment is reproducible and a responsive measure.(22) It is frequently used in both animal and human research studies. A major limitation to its use in clinical practice is its inability to discriminate patients with cough from healthy subjects.(22) Another limitation is that capsaicin dilutions need to be made frequently due to its instability in solution in contrast to other challenge tests such as methacholine. The test also needs to be performed in a ventilated room. The utility of cough reflex sensitivity tests in clinical trials is subsiding because they do not consistently reflect the efficacy of therapy from the patient's perspective. Its use in future is likely to be limited to research studies investigating the mechanism of action of anti-tussive therapy. It may be particularly useful in drug development when specific cough reflex pathways can be investigated. The challenge for the future is to develop methodology that can reliably discriminate healthy subjects from those with cough. This may be possible by using higher concentrations of tussive agents than currently used.(23)

Cough Frequency Monitors

Cough frequency assessment is considered the gold-standard by many for the objective assessment of cough. Until ten years ago, the development of cough monitors was limited by the recording capacity of tape recorders and poor battery life. The development of MP3 recorders overcame hardware limitations, and therefore the focus turned to the development

of software for automated cough detection. There has been significant progress in the development of automated cough detection software, but with mixed results. Many cough monitors have insufficient accuracy for cough detection, and therefore their use is limited or they are not used at all, such as the Hull Automated Cough Monitor, LifeShirt and Pulmotrack.(24-26) A particular challenge has been the discrimination of cough sounds from speech and other noise. Two cough monitoring systems have demonstrated good validity and are being used more widely in clinical trials, the Leicester Cough Monitor (LCM) and the VitaloJak. They differ in their approach to cough detection; the VitaloJak requires manual assessment of cough recordings, and the LCM is largely automated.

VitaloJak

The VitaloJak consists of two microphones (contact and free-field) and a MP3 recorder.(27) A condensed version of the recording is assessed manually to listen for cough sounds. The condensed 24-hour cough recording is on average 1.5 hours long. The accuracy of this monitor is dependent on the observer conducting the manual counting and, in experienced hands, it is very good.(27) A limitation of manual assessment is that it is labour-intensive and time-consuming, which adds to the cost. The VitaloJak has largely been used in one centre. A comparison of the characteristics of the VitaloJak and LCM is reported in Table 2. The characteristics are remarkably similar, despite the very different approaches to cough detection.

Leicester Cough Monitor (LCM):

The LCM comprises of a free-field microphone and a MP3 recorder.(28) Cough detection is largely automated using specifically designed software. This involves minor refinement by an operator (5 minutes per 24-hour recording). The sensitivity and specificity for cough

detection is very good.(28;29) The LCM has been used in single and multi-centre clinical trials.(30;31)

The relationship between objective cough frequency and subjective measures of cough

The relationship between objective cough frequency and subjective measures of cough such as VAS and HRQOL is weak to moderate.(32) This reflects the different aspects of cough assessed by these tools such as perception vs. actual frequency. The poor relationship does not imply that cough frequency monitoring is inaccurate for the detection of cough. The accuracy of automated cough monitors is established by comparison to manually counted recordings.(28)

Cough frequency monitors in the clinical setting

Cough frequency monitors are now sufficiently practical and validated for use in the clinic and clinical trials. The automation of cough monitoring has facilitated this. Patients with chronic cough, cough on average every two minutes in a 24 hour period (Figure 2). This contrasts with healthy subjects who cough on average every thirty minutes. Cough has a diurnal pattern in both disease and health states; cough is significantly reduced at night. In patients complaining of cough, the pattern and frequency of cough is very similar irrespective of underlying causes such as gastro-oesophageal reflux and cough variant asthma. In the authors' experience, the frequency of cough in patients with chronic lung diseases such as classic asthma, COPD and IPF depends on the prominence of cough as a symptom. In some patients, the frequency can be as high as those with idiopathic chronic cough. Cough monitors are the best tools to discriminate patients with cough from healthy subjects.

The utility of cough monitor in clinical practice has not been established. The severity of cough can simply be assessed by asking the patient but disadvantages of this are some patients and clinicians may be poor judges of symptom severity. Cough monitors can potentially be used to validate the presence of cough. They can also be used to quantify the response to therapy. They have been used in the research setting to assess the temporal relationship of cough with episodes of gastro-oesophageal reflux; the clinical usefulness of this has not been established.(33) The benefits of cough monitoring technology in the clinic need further investigation. Cough monitors however are considered an important end-point in clinical trials. The strength of cough monitors is their objectivity and that they can discriminate healthy subjects from those without cough. This may be useful for selecting patients for clinical trials. Cough frequency has been reported to be a repeatable measure in patients with stable chronic cough. In contrast, in acute cough, cough frequency is not repeatable due to natural recovery.(6) The rate of improvement in cough frequency may be a better measure in such patients.

Cough frequency monitors as a study endpoint

Cough frequency can be expressed by a range of outcome measures. For example, absolute counts vs. coughs per hour. Cough can be assessed during daytime, night time or 24 hours. It is perhaps better to express change in cough frequency as a percentage or fold change, rather than absolute change, since it has a wide range. An advantage of using cough frequency measures to determine the sample size of studies is that considerably fewer subjects are required in comparison to subjective outcome measures, such as HRQOL. This is due to the comparatively larger change in cough frequency required to demonstrate a minimal important difference.(6) For example, in acute cough, the minimal important difference for cough frequency has been reported as a 54% reduction.(6)

Cough Intensity

The intensity of cough may also be relevant to the impact on an individual, in addition to the frequency. Little is known about cough intensity and its importance to patients. It can be assessed subjectively with VAS or objectively with physiological measures such as cough flow, oesophageal pressure or electromyography. Flow is the most practical physiological measure since it is non-invasive and relatively easy to perform. However, its limitation is that it is not ideal for continuous monitoring in an ambulatory setting. It may be possible to assess cough intensity with sound.⁽³⁴⁾ Further studies are needed to determine whether cough sound is a valid measure of cough intensity, its relationship with subjective measures and clinical relevance.

Conclusion

A number of tools are now available to assess cough. It is likely that a combination of subjective and objective assessment is necessary to assess cough comprehensively since each tool assesses very different aspects. For subjective assessment, the VAS is ideal for use in the clinic since it is practical, and it can be used to communicate the severity of cough to other clinicians and for longitudinal observation. It is also ideal for use in clinical trials. The VAS should be complemented by HRQOL assessment to assess impact. HRQOL questionnaires for cough are the most validated of all cough assessment tools. The LCQ and the CQLQ are the most widely used for adult patients with chronic cough. It is arguable that the primary outcome measure of clinical trials should be objective, and cough frequency monitors are best placed for this. Cough frequency monitors are increasingly being used in clinical trials. The clinical experience of using cough monitors to date is that they are practical and valid. They should always be complemented by assessment of HRQOL since a

reduction in objective cough frequency without subjective improvement would not be considered clinically important. Further work is necessary in a number of areas to improve the utility of cough assessment tools. The investigation of the minimal important difference and more precise sample size estimations are good examples. The assessment of cough in chronic lung disease such as chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis is likely to be very fruitful.

Table 1. Cough measurement tools.

SYMPTOMS	HRQOL	OBJECTIVE	
		Cough Reflex Sensitivity	Cough Monitors
VAS	LCQ	Capsaicin	LCM
CSS	CQLQ	Citric Acid	VitaloJak
CSD		Fog	
		Tartaric acid	

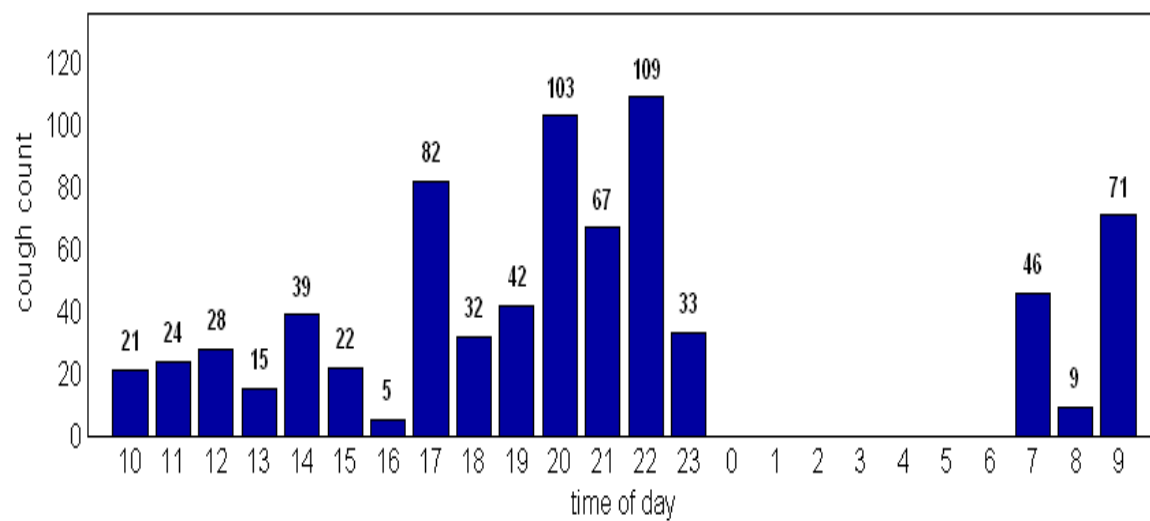
HRQOL: health related quality of life, VAS: visual analogue scales, CSS: cough severity score, CSD: cough severity diary, LCQ: Leicester Cough Questionnaire, CQLQ: cough specific quality of life questionnaire, LCM: Leicester Cough Monitor.

Table 2. A comparison of the characteristics of Leicester Cough Monitor vs. VitaloJak

	Leicester Cough Monitor (LCM)	VitaloJak
Hardware	External microphone and MP3 recorder	External microphone and MP3 recorder
Recording duration	24 Hours	24 Hours
Analysis method	Automated software	Manual
Operator time (mean/ per 24-hr recording) (6;27)	5 min	87 min
Association with subjective measure (HRQOL, LCQ) (correlation coefficient)(32;35)	-0.60	-0.62
Cough frequency (per hr) Healthy subjects (29;36) Chronic cough (29;37) Acute cough URTI (6;38) COPD (29;36)	 1 20 15 9	 1 17 12 9

LCQ: Leicester Cough Questionnaire (patients with chronic cough); HQROL: health related quality of life; COPD: chronic obstructive pulmonary disease; URTI: upper respiratory tract infection. Cough frequency recordings per 24-hours.

Figure 1. 24 Hour frequency in a patient with chronic cough.



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